REMARKS

Claims 1-3 are pending in the instant application. Claim 1-3 have been rejected. Claim 1 has been amended. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Rejection of Claims Under 35 U.S.C. §103

The Examiner has maintained the rejection of claims 1-3 under 35 U.S.C. §103(a) as being unpatentable over Coligan et al. (Current Protocols in Immunology, Green Publishing Associates and Wiley-Interscience, New York, 1991; pages 2.1.1-2.1.3, 2.1.9-2.1.11, and 2.1.17-2.1.22) in view of U.S. Patent 5,077,216, Zwaldo et al. (1987) (IDS Reference BA), and newly cited Zwaldo et al. (1992) (IDS Reference AX) for the reasons set forth in the Office Action mailed 1/18/03.

The Examiner suggests that Applicants' arguments were not persuasive because an argument against obviousness cannot be established by attacking the cited references individually when the rejection is based on the combination of references. Further, the Examiner finds that the instant claims are drawn to a method for monitoring an inflammatory response cascade in a patient by detecting CD163 and that Zwaldo et al. (1987) teach monitoring the level of RM3/1 antigen at different inflammatory stages starting immediately after inflammation (0 hr) as shown in Figure 3 and at pages 299, 301 and 303. Moreover, the Examiner suggests that Zwaldo et al. (1992) teaches monitoring the appearance of RM3/1-positive macrophages in blood between 24 and 72 hours post inflammatory response and that it would be immediately obvious to one of skill in the art that Zwaldo et al. teach that the

detection of the expression of RM3/1 (*i.e.*, CD163) is useful for monitoring an early signaling even in an inflammatory response. Further, it is suggested that it would have been obvious to use the MAC2-158 and MAC2-48 antibodies as capture antibodies taught in the '216 patent and the antibodies taught by Zwaldo et al. as the detection antibody in the ELISA taught by Coligan et al. to have a method for monitoring the course of an inflammatory condition or inflammatory response in a patient by detecting the levels of CD163 in a biological sample as taught by Zwaldo et al.

Applicants respectfully traverse this rejection.

In an earnest effort to advance the prosecution of this application, Applicants have amended claim 1 to recite the window of time in which CD163 levels are detected to effectively monitor an *early* signaling event in an inflammatory response cascade in a patient. The findings presented in the present application indicate that CD163 is one of the earliest markers of an acute inflammatory response that can be detected in plasma (see page 11, lines 12-15 of the present application). The data show that CD163 levels increase at 60 minutes following cardiopulmonary bypass and return to slightly below baseline levels on post-operative day 1 (see page 10, lines 8-11) and CD163 levels peak at 1 to 2 hours and remain elevated at 12 hours compared to baseline levels in healthy volunteers given LPS infusions (see page 10, lines 30-35). Accordingly, claim 1 has been amended to recite that the inflammatory response cascade is monitored by assaying for the levels of CD163 in a sample from a patient known to have or suspected of having been exposed to an inflammatory stimulus using a CD163 immunoassay wherein a detectable elevation in the level of CD163 within 1 to 12 hours of exposure to the

inflammatory stimulus is indicative of an early signaling event in the inflammatory response cascade in the patient. Support for these amendments is found at page 11, lines 17-20 and page 10, lines 8-11 and lines 30-35.

MPEP § 2143 states that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references when combined must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination must both be found in the prior art, and not based on the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In view of amended claim 1, the combined teachings of Coligan et al., U.S. Patent 5,077,216, Zwaldo et al. (1987) and Zwaldo et al. (1992) fail to meet these three basic criteria. First, the combined references fail to suggest or motivate one of skill in the art to detect CD163 levels within the first 1 to 12 hours of the inflammatory response as Coligan et al. and patent '216 do not teach temporal regulation of CD163 and, while Zwaldo et al. (1992) teach that RM3/1 positive monocytes increased in blood at 24 and 72 hours after exposure to dexamethasone, this reference in view of the teachings of Zwaldo et al. (1987) would not provide motivation for the skilled artisan to modify the teachings in the art to monitor CD163 levels before 24 hours as Zwaldo et al. (1987) teach away from the present invention in

demonstrating that CD163 is preferentially expressed by macrophages appearing late in the inflammatory response in acute inflammatory tissue and to varying degrees in chronic inflammation, and RM3/1 macrophages actually decrease during the onset of inflammation between time 0 and day 2 (see page 303, 2nd full paragraph and Figure 3).

Second, elevated levels of CD163 at 1 to 12 hours of exposure to the inflammatory stimulus is insight into the inflammatory response that was contrary to the understandings and expectations of the combined referenced teachings disclosing temporal regulation of CD163. Zwaldo et al. (1987) teach that CD163 levels decrease during the onset of inflammation between 0 and 48 hours. The teachings of Zwaldo et al. (1992) inconsistently teach that CD163 levels are elevated at 24 and 72 hours. Thus, in view of the combined teachings of these references, it would be difficult for one of skill in the art to have a reasonable expectation of successfully monitoring an early signaling event in an inflammatory response cascade during the early time frame of 1 to 12 hours as the cited references provide contradictory results regarding the expression of CD163 at later time points in the inflammatory response.

Finally, the cited references when combined fail to teach or suggest all the claim limitations as they fail to teach the limitation of detecting CD163 levels within the first 1 to 12 hours of the inflammatory response.

Because the cited references fail to establish a *prima facie* case of obviousness, withdrawal of this rejection is respectfully requested.

II. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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